REMARKS/ARGUMENTS

In response to the Office Action of November 4, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40, 42 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on September 22, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from consideration on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer markers of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendment to the specification made herein.

The paragraph at page 24 has been amended to correct a

typographical error (luymph to lymph).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to clearly indicate that the biopolymer markers, SEQ ID NOS:1 and 4, evidence a link to Type II diabetes. This amendment is supported by the specification as originally filed; page 35, lines 14-18, disclose that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer markers which evidence a link to at least one specific disease state and page 46, line 14 to page 47, line 2 identify SEQ ID NOS:1 and 4 as biopolymers related to the specific disease, Type II diabetes.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 39 has also been amended to clearly indicate how the presence of the claimed biopolymer marker is determined from mass spectral profiles. The changes to claim 39 find basis throughout the original disclosure, see, for example, page 38, line 10 to page 40, line 16 and Figures 1-4.

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Claim 42 has been amended to clarify that the recited Markush group is a group of different mass spectrometric techniques.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NOS:1 and 4 a search of these claims would encompass these specific sequences. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer markers of SEQ ID NOS:1 and 4 are found to be novel, methods and kits limited to their use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on May 16, 2005, stands rejected under 35 USC 101 because the claimed invention allegedly has no apparent or disclosed specific and substantial credible utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a substantial credible utility.

The Examiner asserts that the instant specification fails to explain the relationship between a polypeptide of SEQ ID NO:1 or SEQ ID NO:4 with Type II diabetes. The Examiner then asks several questions regarding the claimed peptides which allegedly must be answered in order for the instant invention to satisfy the requirements of 35 USC 101. Is the up or down regulation of the marker relative to categorization of disease state? Is the presence/absence of the polypeptide of SEQ ID NO:1 or the polypeptide of SEQ ID NO:4 indicative of a disease? What is the critical level of up or down regulation that is predictive of a disease state or predictive of Type II diabetes? The Examiner concludes that it appears in order to practice the claimed invention a skilled practitioner would have to engage in significant further research to determine if peptides of SEQ ID NO:1 or SEQ ID NO:4 are absent or present or strongly present in all or any tissue samples of a person suspected of having Type II diabetes, or is up or down regulated in disease in order to establish if the claimed peptide can be used as a marker for Type II diabetes.

Applicants respectfully submit that the Examiner's statements reveal an incomplete understanding of the claimed invention as the invention can be used by one of skill in the art for two distinct purposes. For example, the instant inventors identified the claimed

peptides (SEQ ID NOS:1 and 4) as markers for Type II diabetes by carrying out the disclosed methods. These identified markers can then be used as markers for Type II diabetes, i.e. by testing unknown samples for the presence of the markers or alternatively the disclosed methods can be used to identify markers in another disease condition. The information disclosed in the instant specification, such as that on page 5, lines 12-20 and page 11, lines 9-20, is disclosed to indicate how the claimed biopolymer markers (SEQ ID NOS:1 and 4) were evaluated and is meant to teach one of ordinary skill in the art how the duplicate the findings of the instant inventors to identify the claimed peptides or other peptide markers.

The relationship between the claimed markers (SEQ ID NOS:1 and 4) and Type II diabetes depends upon the differential expression of the claimed markers between patients having Type II diabetes and patients determined to be normal with regard to Type II diabetes (for example, see page 1, lines 5-13, page 38, lines 17-21 and page 11, lines 9-20 of the instant specification as originally filed). One of ordinary skill in the art would be able to determine the nature of this relationship from simple observation of a gel such as that shown in Figure 1; for example, in the instant case, the claimed peptides are present in normal samples and absent in Type II diabetes however in another disease condition a marker may be

in present in the disease and absent in the normal or present in both disease and normal at different levels.

The instant inventors isolated the claimed peptides (SEQ ID NOS:1 and 4) by carrying out the disclosed protocols (chromatography and mass spectrometry) on samples obtained from Type II diabetes patients and healthy patients, noted the expression in normal patients relative to lack of expression in Type II diabetes patients, subjected the noted expression pattern to the criteria as disclosed at page 11, lines 9-20 of the instant specification, decided that the peptides show stronger expression in the normal patients as compared to expression in the Type II diabetes patients, and, thus identified the peptides (SEQ ID NOS:1 and 4) as markers linked to, and possibly predictive of Type II diabetes. The mass spectral profiles established for the claimed biopolymer markers are presented in Figures 2 and 4 (SEQ ID NO:1 in Figure 2 and SEQ ID NO:4 in Figure 4). It is important to note that mass spectral profiles are reproducible, many have been published for reference purposes. Thus, the mass spectral profiles of the claimed peptides as disclosed in Figures 2 and 4 are intended to be used as references for evaluation of unknown samples, and, as such are to be considered diagnostic tools. Accordingly, contrary to the Examiner's assertions, a skilled practitioner would not be required to engage in significant further

research to establish if the claimed peptides can be used as markers for Type II diabetes since the instant specification discloses the mass spectral profiles of the claimed peptides (Figures 2 and 4) and teaches their use a diagnostic tool.

The Examiner asserts that the state of the art is such that it does not recognize any specific association of the polypeptide of SEQ ID NO:1 or SEQ ID NO:4 with any particular disease state in general or with Type II diabetes in particular.

As was explained in the previous response filed on May 16, 2005, while the art does not recognize a specific association between the claimed peptides (SEQ ID NOS: 1 and 4) and Type II diabetes, the art does recognize, contrary to the Examiner's allegation, an association between fibronectin and Type II diabetes.

Fibronectin is a key component of the extracellular matrix; functioning, through a series of binding domains, to maintain normal cell morphology via organization of cell attachment to the extracellular matrix. Fibronectin is particularly prone to fragmentation since the regions between the binding domains are highly susceptible to proteolysis. Fibronectin fragments are known to have functions not found in the intact protein, such as exerting affects on the proliferation and migration of endothelial cells (see attached article of Grant et al. Diabetes 47:1335-1340 1998;

reference 1 which contains the information about fibronectin disclosed in the instant paragraph).

Additionally, increased proteolysis is known to contribute to the pathologic process of Type II diabetes (Comment by Luc Tappy on Gastadelli et al. Diabetes 49:1367-1373 2000; as accessed from the internet; reference 2).

Furthermore, excess fibronectin produced in diabetes is theorized to be available for fragmentation (Grant et al. Diabetes 47:1335-1340 1998; reference 1). Grant et al. (Diabetes 47:1335-1340 1998; reference 1)hypothesized that the formation of abnormal fibronectin fragments *in vivo* could facilitate aberrant angiogenesis, as seen in such conditions as proliferative diabetic retinopathy.

The instant inventors hypothesize that the stronger expression of the fibronection precursor in patients considered to be normal with regard to Type II diabetes when compared to expression seen in patients with a history of Type II diabetes indicates that fragmentation of fibronectin may occur during the diabetic disease process.

Considering that there is a known increase in proteolysis in Type II diabetes and that fibronectin is particularly sensitive to such proteolysis (degradation into fragments) and further considering the suggestion in the art that fibronectin fragments

may be involved in diabetic processes such as proliferative retinopathy, a skilled artisan would find the hypothesis and data disclosed in the instant application entirely plausible, and thus would reasonably link the claimed biopolymer markers (SEQ ID NOS: 1 and 4) with Type II diabetes.

The Examiner uses two hypothetical examples which allegedly support her position. The first is a hypothetical specification which claims a peptide that is expressed in colon cancer and not expressed in healthy colon tissue. This hypothetical specification does not disclose the biological activity of the claimed peptide. The Examiner asserts that the claimed peptide in this hypothetical example has utility and is enabled as a colon cancer marker. Alternatively, the Examiner also suggests a hypothetical example in which a claimed peptide is expressed at specific altered levels in colon cancer as compared to healthy colon tissue. The Examiner asserts that one skilled in the art would immediately recognize that the claimed peptide in this hypothetical example would be useful as a colon cancer marker. However, the Examiner insists that the instant situation does not follow the fact pattern in either hypothetical example.

The instant specification discloses that the claimed markers (SEQ ID NOS:1 and 4) are present in normal patients (patients who were determined to be healthy in regard to Type II diabetes) but

are not strongly present in Type II diabetes patients. Band 1 of Figure 1 (as originally filed and as attached to the declaration filed herewith) contains the fibronectin precursor fragments. Band 1 is clearly evident in lanes 1-4, all of which contain samples obtained from normal, healthy patients. Band 1 is not observed in lanes 5-9, all of which contain samples obtained from Type II diabetes patients. Band 1 of Figure 3 (as originally filed and as attached to the declaration filed herewith) contains the fibronectin precursor fragments. Band 1 is clearly evident in lanes 7-10, all of which contain samples obtained from normal, healthy patients. Band 1 is not observed in lanes 2-6, all of which contain samples obtained from Type II diabetes patients. Peptides identified as present in normal patients as compared with patients having a disease are said to be predictive of the disease (see page 11, lines 9-13 of the instant specification as originally filed). Thus, one of ordinary skill in the art reviewing the data would recognize the claimed fibronectin precursor fragments (SEQ ID NOS:1 and 4) would be useful as predictive markers for Type II diabetes. Accordingly, although the Examiner's hypothetical examples appear to be limited to markers found in a disease state, the criteria or reasoning for identifying a marker, expression vs. absence of expression, in the instant situation is the same as the Examiner's hypothetical example.

The Examiner also asserts that if the claimed peptides are not diagnostics for Type II diabetes, then it is not obvious why they are named markers.

Applicants respectfully disagree with the Examiner's assertion.

The claimed biopolymer markers (SEQ ID NOS:1 and 4), although not specifically diagnostic of any condition, are differentially expressed in tissue samples from Type II diabetes patients and normal, healthy patients. Thus, according to the instant invention the criteria for labeling a peptide a "marker" is differential expression in disease vs. normal. Stedman's Medical Dictionary defines the term "marker" as a physiological substance, that when present in abnormal amounts in the serum may indicate the presence of disease (see attached definition as accessed from the internet at dictionary.com; reference 3). Thus, it is acceptable in the art to identify a protein as a marker based simply on the presence of abnormal amounts, no extension validation is required. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103 (4):433-446 1996; reference 4) identify homovanillic acid as a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in

age-matched controls.

Thus, Applicants respectfully submit that, contrary to the Examiner's assertion, it is obvious why a worker of ordinary skill in the art would refer to the claimed peptides (SEQ ID NOS:1 and 4) as markers for Type II diabetes.

The Examiner further questions if a peptide of SEQ ID NO:1 was found in a sample obtained from a patient what would that mean to a skilled practitioner? Does it mean that the patient has Type II diabetes, or is at risk for developing the disease? The Examiner concludes that at present, it appears that the only information obtained from identifying the presence of marker SEQ ID NO:1 or of SEQ ID NO:4 is the determination of a link to Type II diabetes.

The instant specification teaches that observed differential expression of a peptide between health and disease identifies it as a disease marker (see Figures 1 and 3 and the instant specification at page 11, lines 9-13) and the prior art teaches that such identification of disease markers is acceptable (see Cheng et al.; reference 4). Since SEQ ID NO:1 was isolated from Band 1 of the gel shown in Figure 1 and Band 1 was observed in normal patients but not in Type II diabetes patients, a skilled practitioner would recognize SEQ ID NO:1 as a potential predictive marker for Type II diabetes. Thus, the instant specification, as originally filed, provides answers to the Examiner's questions.

In order to satisfy the requirements of 35 USC 101, an applicant must show that the claimed invention is "useful" for some purpose either explicitly or implicitly (see MPEP 2107.01).

The showing of a link between a peptide and a disease implies the potential for use of the peptide for diagnosis and/or therapeutics of the disease. For example, Blennow et al. (Dementia 6(6):306-311 1995; reference 5) suggest, based on differential expression, that chromogranin in cerebrospinal fluid has a potential as a biochemical marker for synaptic degeneration in AD type I.

Thus, even if the only information obtained from identifying the presence of marker SEQ ID NO:1 or of SEQ ID NO:4 is the determination of a link to Type II diabetes, Applicants respectfully submit that such information would be enough to establish the utility of the instant invention since the showing of a link between the claimed peptides (SEQ ID NOS:1 and 4) and Type II diabetes implies the potential for use of the claimed peptides for diagnosis and/or therapeutics of Type II diabetes.

Claim 1 is drawn to biopolymer markers (SEQ ID NOS:1 and 4) which are disclosed as predictive of and/or linked to Type II diabetes in the specification as originally filed (see page 46, line 14 to page 47, line 2, Figures 1-4, original claims 1 and 2). Figures 1 and 3 evidence the presence of the fibronectin precursor

(including the claimed peptides SEQ ID NOS:1 and 4) in samples obtained from normal patients (determined to be healthy with regard to Type II diabetes) and the absence of the fibronectin precursor in samples obtained from Type II diabetes patients. Clearly, the claimed biopolymer markers (SEQ ID NOS:1 and 4) represent a diagnostic tool for Type II diabetes. Thus, Applicants respectfully submit that no specific biological role for the peptides or information of how to manipulate for a desired clinical effect is required to prove that the claimed biopolymer markers are useful. The showing of "differential expression" of the claimed biopolymer markers is sufficient to establish the credibility of the stated utility for the claimed biopolymer markers. Thus, Applicants also explicitly show that the claimed biopolymer markers are useful.

However, the Examiner apparently does not find this use credible.

It has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Claim 1 has been amended to recite that the isolated biopolymer markers SEQ ID NOS:1 and 4 evidence a link to Type II diabetes.

At pages 46-47, the instant specification as originally filed, discloses that SEQ ID NOS:1 and 4 are fragments of the fibronectin precursor protein.

An objective of the instant invention is to evaluate samples containing a plurality of biopolymer markers for the presence of disease-specific markers which evidence a link to at least one specific disease state (see the instant specification as originally filed at page 35, lines 14-18). According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 6). Applicants respectfully assert that the instant specification fully supports a connection and/or an association of the claimed biopolymer markers (SEQ ID NOS:1 and 4) with Type II diabetes. The claimed biopolymer markers (SEQ ID NOS:1 and 4) were identified as related to Type II diabetes by carrying out the protocols disclosed in the specification (see page 46, line 12 to page 47, line 2 of the instant specification as originally filed). The data presented in Figures 1 and 3 (as originally filed and as attached to the declaration filed herewith) clearly evidences that the claimed biopolymer markers (SEQ ID NOS:1 and 4) were found to be differentially expressed between Type II diabetes patients and patients determined to be normal with regard to Type II diabetes. Thus, Applicants assert that the claimed

biopolymer markers (SEQ ID NOS:1 and 4) are useful for diagnosis and treatment of Type II diabetes (an "asserted" utility).

Accordingly, Applicants respectfully submit that it is improper for the Examiner to simply dismiss the evidence presented by the instant specification (discussed above and in previous Responses) and continue to maintain the assertions that the instant application provides no utility for the claimed biopolymer markers (SEQ ID NOS:1 and 4).

Furthermore, the Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of USC 101 are met solely by Applicants' above assertion regarding the use of the claimed biopolymer markers (SEQ ID NOS:1 and 4).

Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13, page 35, lines 14-18, page 46, line 14 to page 47, line 2 and Figures 1-4).

The claimed biopolymer markers (SEQ ID NOS:1 and 4) does not evidence a link to a myriad of unspecific diseases but rather evidence a link to a specific disease, Type II diabetes, thus, the invention has a "specific" utility.

The differential expression of the claimed biopolymer markers

(SEQ ID NOS:1 and 4) between Type II diabetes and "normal" (patients determined to be normal with regard to Type II diabetes) physiological state links the biopolymer markers to Type II diabetes.

Based upon her comments, the Examiner apparently believes that differential expression is an insignificant observation to consider when evaluating a peptide as a potential marker. Applicants respectfully disagree with the Examiner's view.

In the search for specific biomarkers, proteins found to be differentially expressed between "disease" and "normal", are frequently identified as potential targets for diagnostics and/or therapeutics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 7). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as observed on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 17-21 of the instant specification as originally filed, and Figures

1 and 3). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is known practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states. For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate

cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate

hyperplasia or prostate cancer. Such linking of markers with disease through differential expression is commonly practiced in proteomics.

The Examiner further indicated that Applicants' arguments are not persuasive for two specific reasons. First, it appears that Applicant's statement that "the presence of the claimed biopolymer markers in a sample is indicative of a link to Type II diabetes" is not supported by the instant specification as filed. The Examiner failed to find any reference that would clearly indicate that the finding of peptides SEQ ID NO:1 or of SEQ ID NO:4 is a sample would be indicative of a link to Type II diabetes. Second, Applicant's explanation of the data as presented in the originally filed Figures 1 and 2 appears to contradict Applicant's own statement because band 1 is clearly presented in lanes 7-9 of Figure 3, which corresponds to normal control patients.

Applicants contend that both of these assumptions are incorrect.

Figures 1 and 3, as originally filed, support the statement "the presence of the claimed biopolymer markers in a sample is indicative of a link to Type II diabetes" since these figures evidence the differential expression of the claimed biopolymer markers between Type II diabetes patients and patients determined to be normal with regard to Type II diabetes. Band 1 is clearly

presented in lanes 7-10 of Figure 3 which correspond to normal control patients, however, this does not contradict any of Applicants' statements since it has been established multiple times in the instant response and in previous responses that the claimed biopolymer markers (SEQ ID NOS:1 and 4) were found in Band 1 which was expressed in the control patients and **NOT** in Type II diabetes patients (for example, see the previous response at page 24, last paragraph).

However, as evidenced by her comments, the Examiner appears to believe that a marker can only be a peptide found in a disease state and not found in a normal physiological state. The Examiner is reminded that the definition of the term "marker" according to the instant invention is not limited to peptides found in a disease state and absent in a normal state (for example, see page 5, lines 9-20 of the instant specification as originally filed). Considering that, in the instant application, the claimed markers (SEQ ID NOS:1 and 4) are found in patients determined to be normal with regard to Type II diabetes, it is in accordance with the invention that the figures do not exemplify SEQ ID NOS:1 and 4 as measurable in patients having Type II diabetes.

Additionally, the Examiner appears to misinterpret the data presented in the figures. Thus, Applicants herein provide the attached Declaration (and figures) under 37 CFR 1.132. in order to

more clearly present the gels from which the claimed biopolymer markers were obtained (SEQ ID NOS:1 and 4). The figures attached to the declaration were produced by scanning the original photograph of the gels. No new matter has been added; the first figure is simply a clearer copy of Figure 1 as originally filed is provided to clarify the presence and/or the absence of the bands. The first figure attached to the declaration is entitled "DEAE 1 (Elution) Normal vs. Diabetes Type II" . The second figure attached to the declaration is simply a clearer copy of Figure 3 as originally filed is provided to clarify the presence and/or the absence of the bands. The figure is entitled "HiQ3 (scrub) Normal vs. Diabetes Type II".

The gels shown in the figures attached to the declaration do not represent new experimentation; the figures show clearer images of the original gels made at the time that the experiments described in the instant specification were first carried out.

Applicants submit that Figures 1-4, as originally filed, are "evidence of record" which supports Applicants' possession of the claimed peptides (SEQ ID NOS:1 and 4) and their relationship to Type II diabetes.

Figure 2 (as originally filed) shows a mass spectral profile obtained from Band 1 of the gel shown in Figure 1. Expression of the claimed peptide (SEQ ID NO:1) was shown, in Figure 1, to be

present in serum samples obtained from normal patients and not present in serum samples obtained from Type II diabetes patients. Thus, the claimed peptide (SEQ ID NO:1) is differentially expressed in Type II diabetes versus normal.

In order to further illustrate this point, Applicants provide the attached declaration with figure entitled "DEAE 1(Elution) Normal vs. Diabetes Type II" which represents Figure 1 as originally filed. The attached figure was produced by scanning the original photograph of the gel. Expression of Band #1 is shown in samples obtained from patients determined to be normal with regard to Type II diabetes (lanes 1-4, as read from the left) and is not shown in samples obtained from Type II diabetes (lanes 5-9). Thus, the claimed peptide (SEQ ID NO:1) is shown to be differentially expressed between Type II diabetes and normal controls. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (SEQ ID NO:1). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

Figure 4 (as originally filed) shows a mass spectral profile obtained from Band 1 of the gel shown in Figure 3. Expression of

the claimed peptide (SEQ ID NO:4) was shown, in Figure 3, to be present in serum samples obtained from normal patients and not present in serum samples obtained from Type II diabetes patients. Thus, the claimed peptide (SEQ ID NO:4) is differentially expressed in Type II diabetes versus normal.

In order to further illustrate this point, Applicants also provide the attached declaration with figure entitled "HiQ3 (scrub) Normal vs. Diabetes Type II" which represents Figure 3 as originally filed. The attached figure was produced by scanning the original photograph of the gel. Expression of Band #1 is shown in samples obtained from patients determined to be normal with regard to Type II diabetes (lanes 7-10, as read from the left) and is not shown in samples obtained from Type II diabetes (lanes 2-6). Thus, the claimed peptide (SEQ ID NO:4) is shown to be differentially expressed between Type II diabetes and normal controls. No new matter has been added; this figure is simply a clearer copy of Figure 3 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (SEQ ID NO:4). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

Furthermore, it has been settled that an applicant is not

required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2164.07 I C).

Figures 1 and 3 establish that the claimed biopolymer markers (SEQ ID NOS:1 and 4) are differentially expressed between Type II diabetes patients and patients determined to be normal with regard to Type II diabetes. As pointed out above, one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Thus, differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease condition, no additional validation or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill in the art would believe, based upon the information in the specification and in light of the knowledge in the prior art, that the claimed biopolymer markers (SEQ ID NOS:1 and 4) are more likely than not to be markers for Type II diabetes.

If an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in

Nelson v. Bowler and Crossley 206 USPQ 881).

The instant invention provides peptides which were determined to be linked to Type II diabetes, thus, unknown samples can be screened for the presence of the peptides in order to link the sample to Type II diabetes. Since new information about the peptide is provided (a link to Type II diabetes), no additional research is required in order to use the peptides a diagnostic tools for identification of the claimed biopolymer markers (SEQ ID NOS:1 and 4) in a sample to link the sample to Type II diabetes.

The incidence of Type II diabetes is increasing in westernized countries as is mortality and morbidity due to its symptoms. Thus, advances in diagnosis and treatment of Type II diabetes are highly desirable and would greatly benefit the population susceptible to Type II diabetes. The instant invention discloses peptides (SEQ ID NOS:1 and 4) which have already been identified as linked to Type II diabetes and thus, represents an advance in diabetes research in its current form; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, contrary to the Examiner's assertion, the instant invention has "real-world" value.

Furthermore, when considering practical utility ("real-world" utility) relevant evidence is judged as a whole for its persuasiveness in linking observed properties to suggested uses (*Nelson v. Bowler and Crossley* 206 USPQ 881).

The instant specification suggests that the claimed biopolymer markers (SEQ ID NOS:1 and 4) are useful for diagnostics and/or therapeutics of Type II diabetes since they were found to be differentially expressed in Type II diabetes versus a normal physiological state Applicants respectfully assert that the observed differential expression is enough evidence such that one of ordinary skill in the art would be reasonably certain of the practical utility of the claimed biopolymer markers (SEQ ID NOS:1 and 4).

Applicants respectfully submit that the Examiner, in asserting that the claimed peptide is only useful for further research, is in a sense labeling the claimed peptide a "research tool". An assessment that focuses on whether an invention is useful only in a research setting does not address whether the invention is in fact "useful" in a patent sense. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (they are useful in analyzing compounds). See MPEP 2107.01. Furthermore, it has been established that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. See MPEP 2107. 01 III and *In re Brana* 34 USPQ2d 1436. Accordingly, a research tool can not automatically be assumed to be without

utility.

The purpose of the patent system is to promote the useful arts. The utility of "research tools" and pharmaceutical inventions in early development has been frequently addressed by the courts.

The situation in the instant case is analogous to that of *Cross v. Iizuka* (MPEP 2107.01 III and 224 USPQ 739). In *Cross*, the Federal Circuit affirmed a finding by the Board of Patent Appeals and Interferences that a pharmacological utility had been disclosed in the application of one party to an interference proceeding. Cross had challenged the evidence in Iizuka's specification that supported the claimed utility. In *Cross*, the Federal Circuit commented on the significance of data from *in vitro* testing that showed pharmacological activity:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.

Thus, even if one of skill in the art followed the Examiner's method for the discovery of biomarkers and considered the instant invention to be only a "first step", they (the claimed peptides) would still be considered to have practical utility according to legal precedent. The disclosed link between the claimed peptides (SEQ ID NOS:1 and 4) and Type II diabetes will concentrate resources and effort into these peptides, thereby providing immediate benefit to the public, especially the population at risk for the development of Type II diabetes.

The Federal Circuit again addressed the utility requirement in *Scott v. Finney* (MPEP 2107.01 III and 32 USPQ2d 1115) and *In re Brana* (MPEP 2107.01 III and 34 USPQ2d 1436). The court found that therapeutic utility under the patent laws is not to be confused with the requirements of the FDA with regard to the safety and efficacy of drugs to be marketed in the United States. The court stated:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove

> utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

The identification of a protein/peptide showing differential expression in Type II diabetes relative to a healthy population puts a researcher one step closer to understanding the pathogenesis of Type II diabetes and thus, also one step closer to improved diagnosis and treatment of Type II diabetes. There is no question that improved diagnosis and treatment of Type II diabetes provides a tangible benefit to society; especially for the population susceptible to the development of Type II diabetes. Thus, the claimed peptides (SEQ ID NOS:1 and 4) have a "real-world" use as is, in their currently available form.

Furthermore, the instant invention provides mass spectral profiles (shown in Figures 2 and 4) of the claimed peptides (SEQ ID NOS:1 and 4) which are intended to be used as references such that the claimed peptides may be identified in unknown samples by comparison of mass spectral profiles (profiles shown in Figures 2 and/or 4 to profiles obtained from unknown samples), thus linking

samples to Type II diabetes based upon the presence of the claimed peptides.

In conclusion, based upon all of the above arguments (and those presented in previous responses), Applicants respectfully submit that one of ordinary skill in the art would immediately appreciate why Applicants regard the claimed biopolymer markers (SEQ ID NOS:1 and 4) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on May 16, 2005, remains rejected under 35 USC 112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art would clearly not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has both a clear asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer

markers (SEQ ID NOS:1 and 4) as markers for Type II diabetes; therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendment to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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